Understanding the role of aqueous solution in chemical reactions: A computational study
Pavlova, A.

Citation for published version (APA):
Pavlova, A. (2013). Understanding the role of aqueous solution in chemical reactions: A computational study
The transfer hydrogenation reaction between the RuTsDPEN model catalyst and formaldehyde was studied in explicit solution with ab initio molecular dynamics. The reaction barriers were computed with constrained dynamics method and important structural changes were analyzed. A study in gas phase, using static geometry optimizations was also done for comparison with solution. It was shown that the reaction mechanism is stepwise and not concerted, in contrast with previous gas phase studies. Also, while previous studies in gas phase and methanol suggested that the NH$_2$ moiety of the catalyst transferred a proton to formaldehyde, here this was done by a water molecule. Further calculations showed that the acid dissociation barrier for the catalyst in water solution is marginally higher than for water. This could explain why the catalyst does not transfer the proton.\(^1\)

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\(^1\) This chapter is based on: “Understanding the role of water in ruthenium catalyzed transfer hydrogenation of ketones.” A. Pavlova, E. J. Meijer, ChemPhysChem, 2012, 3492-3496, DOI: 10.1002/cphc.201200454
3-1 Introduction

Asymmetric hydrogenation of C=O and C=N double bonds, creating stereoselective centers, is one of the most essential transformations in chemistry. Although stereoselective transfer hydrogenation is of immense interest for pharmaceutical industry, the development of efficient asymmetric catalysts for this reaction started less than two decades ago. The pioneering research on this topic was done by Noyori and co-workers [1–4] who had developed several chiral ruthenium based catalysts. One of the most efficient catalysts uses p-cymene and TsDPEN ligand [2; 5] and is shown in Scheme 3.1a. This catalyst efficiently catalyzes asymmetric transfer hydrogenation of various aromatic ketones, using 2-propanol as both solvent and hydrogen donor under mild conditions.

Unfortunately, transfer hydrogenation with 2-propanol is reversible. Therefore, full conversion of the reactant is not possible and the enantiopurity of the product will deteriorate with time [2; 5]. A mixture of formic acid and triethylamine as hydrogen donor and solvent appears as an attractive alternative, not suffering from the contamination effect. However, in practice, it is not yet a feasible alternative, as the reaction has been sluggish with the original Noyori catalysts [3; 5]. Recently, Xiao and coworkers discovered that using formate in water as hydrogen donor greatly enhances the reaction rate of the RuTsDPEN catalyst, without the loss of enantioselectivity [6–8]. A full molecular understanding of this is lacking. In view of this it is of fundamental importance to further elucidate the role of the solvent in improving the rate of ruthenium catalyzed transfer hydrogenation. Here we focus on aqueous solvent conditions. Understanding the role of water as a solvent in catalytic processes is also of generic importance as water is an environmentally friendly and safe solvent and plays an essential role in mimicking biocatalytic mechanisms.

Theoretical calculations [9–14] and experiments [2; 11; 14–18] have already provided some fundamental insight on the mechanism of transfer hydrogenation with ruthenium catalysts. Various independent studies showed that in gas phase, the transfer hydrogenation with a ruthenium catalysts proceeds through a concerted transition state, (Scheme 3.1b) [9–12]. Further studies revealed that protic solvents can play an important role in a transfer hydrogenation reaction by mediating the proton transfer [13] or by stabilizing the ketone...
substrate with strong hydrogen bonds [14]. In the case of aqueous transfer hydrogenation, a secondary kinetic isotope effect is observed [14], suggesting the involvement of water molecules in the mechanism. Furthermore, theoretical calculations with one water molecule give significantly reduced reaction barrier [14]. However, a proper understanding of the role of the solvent requires a model that incorporates a full representation of the solvent with explicit water molecules. We addressed this by performing an ab initio molecular dynamics study of this reaction in explicit water solution using a model ruthenium catalyst and substrate.

### 3-2 Methods

Inter-atomic interactions were modelled using the Kohn-Sham formulation [19] of density functional theory (DFT) [20], employing the BLYP density functional [21; 22]. BLYP combines a gradient-corrected term for the exchange energy as proposed by Becke with a correlation energy term proposed by Lee, Yang, and Parr. This approach provides an accurate description of ruthenium catalyzed transfer hydrogenation [12] and a realistic representation of liquid water [23; 24]. The Kohn-Sham orbitals were expanded in a plane-wave basis set that included waves up to an energy of 70 Ry. Pseudopotentials were used to restrict the number of electronic states to those of the valence electrons. The interaction with the core electrons is taken into account using semi-local norm-conserving Martins-Troullier pseudopotentials [25; 26]. The Ru pseudopotential was of the semi-core type and included the highest s-, p- and d-shell electrons as valence electrons. The pseudo potential the cut-off radii for s, p and d terms were 1.10, 1.20, 1.24 a.u. respectively for the ruthenium atom. For S, C, N, O and H atoms the pseudopotential cut-off radii for the s term were 1.34, 1.23, 1.12, 1.10, and 0.50 a.u., respectively. The pseudopotentials for S, C, N and O also used the same cutoff for the p term as for the s term. In addition, a d term with a cutoff of 1.34 a.u. was employed for the sulfur atom. The CPMD program package was used for all calculations [27].

The catalyst model, as shown in Scheme 3.2, consisted of a ruthenium atom with a benzene ring replacing the cymene ligand, and the 1-amino-2-methylsulfonamide-ethane ligand was used instead of the TsDPEN ligand. Formaldehyde was chosen as the substrate since it is the smallest compound with a C=O double bond. Simplified versions of the catalyst and the substrate were used due to the high cost of DFT calculations. This model keeps the essential characteristics of the catalyst and the reactant.

The aqueous solvent was represented by placing the model catalyst with 54 water molecules in a body-centered-cubic (bcc) periodic box, providing two solvation shells. The reaction in explicit water solution was studied with Car-Parrinello molecular dynamics [28]. Deuterium was used instead of hydrogen in order to use a larger time step. In our calculations we used a fictitious mass of 600 a.u., which has been shown to provide a sufficiently accurate description of water, and allowed for time step of 0.12 fs [24]. The simulated temperature was 350 K, which is 37 degrees higher than the experimental conditions, for a more accurate description of water [24]. The temperature was imposed with Nosé-Hoover
thermostat [29; 30]. A frequency of 500 cm$^{-1}$ was used. The bcc cell volume was 2.0 nm$^3$, consistent with the experimental density data for the catalyst [15], water and formaldehyde.

Chemical reactions occur on a timescale that is out of range for today’s ab initio molecular dynamics simulations. Therefore, the reaction was enforced by the constrained dynamics method [31]. The reaction coordinate, Q, was chosen as the asymmetric stretch Ru-H-C. That is the distance between the transferred hydride and the ruthenium minus the distance between the transferred hydride and the carbonyl carbon, see Scheme 3.2b. We assumed that since the hydride transfer part of the reaction is more difficult than the proton transfer part, this reaction coordinate should be close to the real one. This was confirmed by calculations of the backward reaction that gave very small hysteresis in the average constrained force. The simulations consisted of 2 ps equilibration runs at chosen points along the reaction coordinate, followed by 10 ps production runs. The averaged constrained force of the production runs was integrated, yielding the free energy profile along the reaction coordinate [31].

![Scheme 3.2: a. The catalyst model used in the simulations. b. The reaction coordinate Q used in the simulations.](image)

The basis set, pseudo potentials and the program package were the same in the gas-phase study as in the aqueous study, in order to fully investigate the effect of implicit solvation. In the gas phase study a single cubic cell with 8.0 nm$^3$ volume was used and the reaction was investigated by constrained geometry optimizations along the reaction coordinate. The transition state was fully optimized at the point with the highest energy. Free energy corrections were calculated and added as in the classical harmonic approximation [32].

3-3 Results and Discussion

3-3.1 Transfer Hydrogenation

Figure 3.1a shows the average constrained force along the chosen reaction coordinate, Q, for the reaction in water solution. The force was sampled between Q values of -1.5 Å and 3.1Å. It was 0 at those values and 17 points were sampled in total. The constrained force is initially negative and its sign changes around Q=0, indicating a transition state at this point. It is also very close to 0 when Q=0.83, this suggests that a second transition could occur at
Figure 3.1: a. Average constrained force for the transfer hydrogenation reaction with error bars. The results for the backward reaction are added for comparison. The backward reaction with the same reaction coordinate could only be simulated from the point just before the proton transfer. The errors in the constrained force were estimated by dividing the 10 ps sampling interval into ten 1ps long samples and calculating the 95% confidence interval. b. The free energy profile of the reaction in water, compared to the one in gas phase.

Figure 3.1 shows the calculated free energy profile in water solution compared to the one in gas phase. The barrier for hydrogenation of formaldehyde was 3.4 kcal/mol in water, which is slightly lower than the gas phase barrier of 5.3 kcal/mol. Those barriers are close to the values reported for another ruthenium catalyst in methanol solution [12] and for gas phase in previous studies [9–12], respectively. The transition state occurs earlier in water solution, around Q=0, which is likely due to the hydrogen bonding effect of water.
Ruthenium Catalyzed Transfer Hydrogenation.

Figure 3.2: Selected snapshots from the simulations, distances shown in Å. The transferred hydride is enlarged and has a darker color. Q= -0.13 Å, Just before the transition state, the hydrogen bond between the formaldehyde oxygen and the amino group of the catalyst is formed. Q=0.83 Å, the hydride is transferred and the hydrogen bond between the substrate and the catalyst is broken, forming a methoxide ion. Q=1.14 Å, a proton has been transferred to the substrate by a water molecule. The formed hydroxide is enlarged, and has a different color.

These observations are in agreement with the kinetic isotope studies that suggest involvement of water [14].

Snapshots of important stages along the reaction pathway are shown in Figure 3.2. At Q=-0.13 Å, just before the transition state, the substrate has formed a hydrogen bond with the NH$_2$ group of the catalyst and two water molecules. Beyond the transition state, the formaldehyde oxygen is still hydrogen bonded to the catalyst. At Q=0.83 Å the oxygen-catalyst hydrogen bond is broken, and the formed methoxide ion is stabilized by up to three hydrogen bonds with water. For Q=0.74 and larger, temporary proton transfers from a water molecule to the formaldehyde oxygen can be observed; these protons return in a few fs. For Q=0.94 these transfers are frequent. When Q=1.14 Å, a proton is permanently transferred to the reactant by a water molecule. Note, the NH$_2$ moiety of the catalyst still retains its proton. We also performed four unconstrained simulations, starting from independent configurations of the Q=0.07 trajectory after the transition state. All four trajectories end in the formation of methanol and all of the reactive trajectories show proton transfer from a water molecule, while the catalyst keeps its proton.

Important distance changes for both water and gas phase simulations are shown in Figure 3.3. Figure 3.3a shows the average NH$_2$-O distance in water compared to gas phase. This hydrogen bond is stronger and is formed earlier in gas phase than in water. In aqueous solution, the substrate is able to form hydrogen bonds with water molecules, in addition to the catalyst. Thus, the effect of the latter hydrogen bond is decreased. There is also a difference in the Ru-NH$_2$ bond between gas phase and solution, see Figure 3.3b. This bond does not change significantly in water solution, while in gas phase it decreases due to the loss of a proton. There are no significant differences for the changes in the C=O bond, as shown in Figure 3.3c.

Electronic structure changes during the reactions were also analyzed with the method
Figure 3.3: Illustration of the important distance changes during the reaction. Solid lines and filled symbols show the average results in solution, dotted lines and empty symbols show the results from static geometry optimizations in gas phase. a. The changes in the NH$_2$-O bond. b. The changes in the Ru-NH$_2$ bond. c. The changes in the C=O bond.

of localized Wannier function centers, (WFC) [33]. This method transforms Kohn-Sham orbitals into Wannier functions. The centers of these functions can be assigned with a chemical meaning, such as being associated with a lone pairs or a bond, depending on their location. The position of WFCs of the electron pair in the N-H bond relatively to the nitrogen is shown in Figure 3.4b. For the solution case, there is no significant change, while for the gas phase case there is a decrease of this distance after the transition state, due to the
Figure 3.4: Calculated positions of WFCs along the reaction coordinate. Solid lines and filled symbols represent averaged results for solvated reaction while dashed lines and open symbols represent results of gas phase reaction. The averages in solution are obtained from snapshots taken every 1 ps. a. WFCs in the carbonyl bond of formaldehyde. b. WFCs in the Ru-NH$_2$ and N-H bonds.

loss of the proton. The difference in the proton transfer mechanism between solution and gas phase also affects the Ru-NH$_2$ bond. In gas phase the electron pair in this bond moves away from the nitrogen and closer to the ruthenium atom after the transition state, whereas in solution there is no significant change in the WFC positions. Figure 3.4a shows changes of WFC positions for the electron pairs in the carbonyl bond of formaldehyde. There is a difference for the electron pair that eventually forms the alcohol bond. In solution, its distance to the carbonyl oxygen starts to decrease after the transition state and goes back to
normal after the proton transfer. This supports the existence of a methoxide intermediate, and suggests that it is formed already after the transition state. There is no significant change for the WFC distances to the carbonyl oxygen in gas phase.

![Figure 3.5](image-url): Optimized methoxide intermediate in gas-phase, stabilized by three water molecules, selected distances are show in Å.

A methoxide intermediate, stabilized by multiple hydrogen bonds, is observed in solution. This methoxide intermediate does not appear in earlier gas phase calculations [9–12; 14] as the model lacks hydrogen-bond donors. Therefore, we investigated if this intermediate could be stabilized in the gas phase by introducing three hydrogen bonded water molecules. We optimized a structure shown in Figure 3.5, which is a local minimum on the potential energy surface according to the frequency analysis. Its energy is -12.6 kcal/mol relatively to the separated molecules.

### 3-3.2 Catalyst Deprotonation

In order to understand the different proton transfer mechanism in water solution, deprotonation of the NH$_2$ group of the ruthenium catalyst without the hydride was studied in water. The water molecule closest to one of the nitrogen protons was selected to receive a proton and the reaction coordinate was the N-H-O asymmetric stretch. The sampling started from the protonated catalyst and the constrained force was sampled between 0.92 Å and -1.08 Å with 0.1 Å intervals.

Figures 3.6a and 3.6b show the constrained force and the free energy profile, respectively. The reaction barrier for deprotonation is 18.6 kcal/mol while the reaction barrier for
Figure 3.6: a. Average constrained force for the deprotonation of the ruthenium catalyst with error bars. b. The corresponding free energy profile of the reaction. c. The average distances of the important bonds during the reaction, the Ru-NH$_2$ bond, and the distances of N and O atoms to the proton.

Protonation is 2.0 kcal/mol. The deprotonation barrier for the catalyst is marginally higher than the dissociation barriers for water, calculated with the same density functional, 17.5-18.1 kcal/mol [34; 35]. This suggests that both water and the NH$_2$ group of the catalyst are equally capable to transfer a proton to the methoxide intermediate. Note, the mechanism is sequential and the hydrogen bond between the catalyst and the reactant is broken after the hydride transfer, but before the proton transfer. This could explain why proton transfer from the catalyst is not observed in our simulations.

Figure 3.6c shows the changes of important distances during the reaction. The N-H
bond is increasing as the O-H bond and the Ru-N bond are gradually decreasing. The changes in the Ru-NH$_2$ bond are similar to the gas phase transfer hydrogenation, where a proton is lost. This bond change could be a reason for the high deprotonation barrier, resulting in proton transfer from a water molecule instead of the catalyst. In addition, hydrogen bonding with water molecules stabilizes the NH$_2^+$ group of the catalyst and could contribute to the reaction barrier.

3-4 Conclusions

Our results suggest that ruthenium catalyzed transfer hydrogenation proceeds differently from that in methanol solution [13] and indicate that previous gas phase studies [9–12; 14] constituted an incomplete model. First of all, the hydrogen bonding between the solvent and the substrate is more important than previously believed. As Figure 3.2 shows, the reactant can have hydrogen bonds with up to three water molecules during the reaction, whereas in methanol solution it remained hydrogen bonded to the catalyst. In contrast to what is seen in gas phase models and in the study in methanol solution, the proton transfer to the substrate proceeds from a water molecule, while the proton of the NH$_2$ group remains on the catalyst. Scheme 3.3 summarizes the mechanism observed in water solution. Calculation of the deprotonation barrier for the catalyst after it transferred the hydride showed that this barrier is marginally higher than the calculated dissociation barrier of water [34; 35]. This could explain why a water molecule transfers the proton instead of the catalyst.

Another important observation is that the transfer hydrogenation is stepwise and not concerted, just as in the theoretical study in methanol [13]. This is also supported by kinetic isotope effect studies [14]. Once the hydride is transferred, the carbonyl oxygen loses its hydrogen bond with the catalyst without receiving a proton, yielding a methoxide intermediate. This intermediate does not appear in the gas phase model. The WFC analysis suggests that methoxide is formed after the hydride transfer transition state, see Figure 3.4a. Apparently, in aqueous solution a methoxide intermediate is sufficiently stable, due to the formation of up to three hydrogen bonds. Hence, a proper model requires incorporating sufficient number of hydrogen bonds. This is supported by the optimized gas phase intermediate shown in Figure 3.5, where the substrate is stabilized by three water molecules. The calculated barrier in aqueous solution, described above, was 3.4 kcal/mol, which is similar to the barrier height of the study in methanol [13] solution, and lower than in gas phase studies [9–12; 14]. Experimental evidence suggests that the barrier of the limiting step is 19.5 kcal/mol at 330 K [14]. If the process studied here is the limiting step, the discrepancy could be partly accounted for by the approximated nature of DFT employed in our model. It is also possible that steric effects are not fully accounted for in our simplified model of the catalyst and the substrate. Alternatively, the limiting step could be elsewhere in the catalytic cycle. Future studies should focus on the catalyst regeneration reaction, in order to determine the rate limiting step.

In summary, our ab initio molecular dynamics simulations show that solvent molecules play an active role in a ruthenium catalyzed transfer hydrogenation reaction converting
Scheme 3.3: The reaction mechanism observed in explicit aqueous solution. In the first step only the hydride is transferred and a methoxide intermediate, stabilized by up to three water molecules is formed. In the second step, a water molecule transfers a proton to the ketone while the NH$_2$ moiety of the catalyst is never deprotonated.

formaldehyde into methanol. In the present case we showed that the reaction in solution may follow a different mechanism than suggested by gas phase calculations or studies in methanol solution. The explicit role of solvent molecules also indicates that a proper understanding of reactions in hydrogen bonded solvents requires computational and experimental studies that probe the reacting species and nearest solvating molecules with atomistic detail.
3-5 References


